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Our Docket No. PDC 119
Your Docket No.

Client/Matter No. 078374/00011

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MESSAGE:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Solomon S. Steiner and Bryan R. Wilson

Serial No.: 09/766,362 Art Unit: 1615

Filed: January 19, 2001 Examiner: Humera Sheikh

For: *DRY POWDER FORMULATIONS OF ANTIHISTAMINE FOR NASAL ADMINISTRATION*

Attachments:
Transmittal Form PTO/SB/21
Fee Transmittal Form PTO/SB/17
Second Substitute Appeal Brief

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PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission	25

Application Number	09/766,362
Filing Date	January 19, 2001
First Named Inventor	Solomon S. Steiner
Art Unit	1615
Examiner Name	Humera Sheikh
Attorney Docket Number	PDC 119

ENCLOSURES *(Check all that apply)*

- [✓] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
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- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
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  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
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- [ ] Petition to Convert to a Provisional Application
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- [✓] Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
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Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Pabst Patent Group LLP		
Signature	Rivka D. Monheit		
Printed name	Rivka D. Monheit		
Date	December 27, 2005	Reg. No.	48,731

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Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($) 0.00

Complete if Known	
Application Number	09/766,362
Filing Date	January 19, 2001
First Named Inventor	Solomon S. Steiner
Examiner Name	Humera Sheikh
Art Unit	1615
Attorney Docket No.	PDC 119

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee ($)	Fee Paid ($)	Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
18 - 20 or HP =	0 x		=		

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee ($)	Fee Paid ($)
3 - 3 or HP =	0 x		=

HP = highest number of independent claims paid for, if greater than 3

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
- 100 =	/ 50 =	(round up to a whole number) x		=

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other:	

SUBMITTED BY

Signature	Rivka D. Monheit	Registration No. (Attorney/Agent) 48,731	Telephone (404) 879-2152
Name (Print/Type)	Rivka D. Monheit		Date December 27, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Solomon S. Steiner and Bryan R. Wilson

Serial No.: 09/766,362 Art Unit: 1615

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For: *DRY POWDER FORMULATIONS OF ANTIHISTAMINE FOR NASAL ADMINISTRATION*

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND SUBSTITUTE APPEAL BRIEF

Sir:

In response to the Notification of Non-Compliant Appeal Brief mailed November 30, 2005 in the above-referenced application, please substitute this Appeal Brief for the one submitted on February 15, 2005 at 3:00 p.m. This is an appeal from the final rejection of claims 1-5, 7-12, 14-18, 20 and 21 in the Office Action mailed July 15, 2004, in the above-identified patent application. A Notice of Appeal was filed on December 15, 2004. The Commissioner was authorized on February 15, 2005 to charge $250.00, the fee for the filing of this Appeal Brief for a small entity, to Deposit Account No. 50-3129. It is believed that no fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, MannKind Corporation.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants, the undersigned, or Appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 1-5, 7-12, 14-18, 20 and 21 are pending and on appeal. Claims 6, 13, and 19 were cancelled in an Amendment filed August 21, 2003. New claims 20 and 21 were added in an Amendment filed April 12, 2004. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

An amendment after final rejection was filed on October 13, 2004. In the Advisory Action mailed December 7, 2004, the Examiner indicated that this amendment would not be entered. The claims were last amended in the amendment filed April 12, 2004. An Appendix sets forth the claims on appeal.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a composition for the nasal administration of a drug in a dry powder form suitable for administration to the nasal region, the dry powder form comprising microparticles having an average particle size of between 10 and 20 microns and comprising the

drug and diketopiperazines. Support for claim 1 can be found in the specification at least at page 2, lines 2-5 and page 3, lines 5-7. Claim 2 depends from claim 1 and defines the drug as an antihistamine, vasoconstrictor, antiinflammatory or analgesic. Support for claim 2 can be found in the specification at least at page 3, lines 1-3. Claim 3 depends from claim 2 and defines the antihistamine as chlorpheniramine or azelastine. Support for claim 3 can be found in the specification at least at page 3, line 1. Claim 4 depends from claim 1 and defines the diketopiperazine as a substitution derivative selected from the group consisting of diketomorpholines, diketooxetanes and diketodioxanes. Support for claim 4 can be found in the specification at least at page 11, lines 8-9 and page 12, line 3. Claim 5 depends from claim 1 and defines the diketopiperazine as being formed by cyclodimerization of amino acid ester derivatives. Support for claim 5 can be found in the specification at least at page 11, lines 20-21. Claim 20 depends from claim 1 and defines the composition as being formed by spray drying. Support for claim 20 can be found in the specification at least at page 6, line 21.

Independent claim 7 defines a drug delivery device for nasal administration comprising (1) a drug in a dry powder form in a dosage formulation for administration to the nasal region, and (2) a device for delivering a measured dose of the drug to the nasal mucosa. The dry powder form comprises microparticles having an average particle size of between 10 and 20 microns and comprises the drug and diketopiperazines. Support for claim 7 can be found in the specification at least at page 2, lines 2-5 and page 3, lines 5-7; page 13, lines 4-10; and claim 7 as originally filed. Claim 8 depends from claim 7 and defines the device as a nasal insufflator. Support for

claim 7 can be found in the specification at least at page 13, lines 4-5. Claim 9 depends from claim 7 and defines the drug as an antihistamine, vasoconstrictor, antiinflammatory, or analgesic. Support for claim 9 can be found in the specification at least at page 3, lines 1-3. Claim 10 depends from claim 7 and defines the antihistamine as chlorpheniramine or azelastine. Support for claim 10 can be found in the specification at least at page 3, line 1. Claim 11 depends from claim 7 and defines the diketopiperazine as a substitution derivative selected from the group consisting of diketomorpholines, diketooxetanes and diketodioxanes. Support for claim 11 can be found in the specification at least at page 11, lines 8-9 and page 12, line 3. Claim 12 depends from claim 7 and defines the diketopiperazine as being formed by cyclodimerization of amino acid ester derivatives. Support for claim 12 can be found in the specification at least at page 11, lines 20-21. Claim 21 depends from claim 7 and specifies that the microparticles are formed by spray drying. Support for claim 21 can be found in the specification at least at page 6, line 21.

Independent claim 14 defines a method of administering a drug to the nasal region of a patient in need thereof, by nasally administering a dry powder suitable for nasal administration. The dry powder comprises microparticles having an average particle size of between 10 and 20 microns. The microparticles comprise the drug and diketopiperazines. Support for claim 14 can be found in the specification at least at page 2, lines 2-5; page 3, lines 5-7; page 13, lines 4-10; and claim 14 as originally filed. Claim 15 depends from claim 14 and defines the drug as an antihistamine, vasoconstrictor, antiinflammatory, or analgesic. Support for claim 15 can be found in the specification at least at page 3, lines 1-3. Claim 16 depends from claim 14 and

defines the antihistamine as chlorpheniramine or azelastine. Support for claim 16 can be found in the specification at least at page 3, line 1. Claim 17 depends from claim 14 and defines the diketopiperazine as a substitution derivative selected from the group consisting of diketomorpholines, diketooxetanes and diketodioxanes. Support for claim 17 can be found in the specification at least at page 11, lines 8-9 and page 12, line 3. Claim 18 depends from claim 14 and defines the diketopiperazine as being formed by cyclodimerization of amino acid ester derivatives. Support for claim 18 can be found in the specification at least at page 11, lines 20-21.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17, and 18 are non-obvious as required by 35 U.S.C. § 103(a) over U.S. Patent No. 5,503,852 to Steiner *et al.* ("Steiner"); and

(2) whether claims 3, 8, 10, 16, 20, and 21 are non-obvious as required by 35 U.S.C. § 103(a) over Steiner in view of U.S. Patent No. 5,690,954 to Illum ("Illum").

(7) ARGUMENT

(a) The Invention

Current administration of antihistamines via intranasal routes in aqueous solution imparts systemic side effects such as somnolence and long lasting, bitter tastes (page 1, lines 13-20). Liquid nasal sprays result in antihistamine penetration into the back of the throat where the antihistamine may be orally absorbed and contribute to the central nervous system effects of

somnolence and the bitter taste experienced by patients (page 1, lines 17-20). The dry powder formulations reduce the systemic side effects of liquid nasal sprays because the drug is maintained in the nasal cavity (page 2, lines 2-3). This is achieved through the selection of microparticles having an average particle size of between 10 and 20 microns formed of drug and diketopiperazines (page 3, lines 5-10) which are retained in the nasal region and not passed into the pulmonary system or the mouth. Particles smaller than 10 microns could cause the composition to pass into the pulmonary region or mouth, resulting in less efficient delivery of the drug and causing undesirable side effects with certain type of drugs, e.g., bitterness in the case of an antihistamine. In addition, since the particles as defined by the claims are retained in the nasal region, lower doses of drug can be administered (page 2, lines 23-26).

(b) Rejections Under 35 U.S.C. § 103

The Legal Standard

As stated in MPEP § 2141, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined (MPEP § 2141 citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)). As noted in *Gillette*, "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." (*Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990)).

In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success (*In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988)). Claims are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims (*In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989)). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). The MPEP explains that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combinations"

(MPEP § 2143.01, quoting *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990)). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references" (*In re Dembiczak* , 175 F.3d 994 at 999 (Fed. Cir. 1999)). The "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination (*WMS Gaming, Inc. v International Game Technology*, 184 F.3d 1339 at 1355 (Fed. Cir. 1999)). "[T]he showing must be clear and particular" (*In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999)). The references themselves must lead those in the art to what is claimed. In this case, there is simply no such teaching.

(i) Rejection of claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17, and 18 under 35 U.S.C. § 103(a) as obvious over U.S. Patent No. 5,503,852 to Steiner et al. ("Steiner")

Steiner

Steiner discloses drug delivery systems suitable for oral or intravenous administration wherein diketopiperazines and their analogs form particles incorporating a drug to be delivered. Steiner discloses drugs that are to be released in the circulatory system following **injection** or after transport from the gastrointestinal (GI) tract following **oral delivery** (column 10, lines 29-31). Steiner describes formulations that are stable in the blood, stomach, or small intestine (column 11, lines 15-49). Steiner does not disclose each and every elements of the claims and thus claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17, and 18 are non-obvious over Steiner.

Claims 1, 2, 4 and 5

Independent claim 1 defines a composition for nasal administration of a drug in a dry powder form. Claim 1 specifies that the composition must be in a form suitable for nasal administration. **Steiner does not disclose drug delivery systems in a form suitable for nasal administration.** Steiner discloses formulations administered in a solution or in the form of a tablet. **Steiner does not disclose dry powder formulations.** Claims are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims (*In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992) and *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989)).

Claim 1 also specifies that the dry powder form comprises microparticles having an average particle size of between 10 and 20 microns. **Steiner does not mention nor suggest a composition of microparticles having an average size between 10 and 20 microns.** In contrast, Steiner discloses administering smaller microparticles, with average diameters between 0.1 and 10 microns for oral or intravenous delivery (col. 4, lines 32-40). This size range is ineffective for improving the nasal administration of drugs. Microspheres below 10 microns will pass into the pulmonary region or mouth, resulting in a less efficient delivery of the drug and cause undesirable side effects with certain type of drugs, e.g., bitterness in the case of an antihistamine. Thus, Steiner does not address any problems associated with nasal administration of drugs.

Steiner teaches away from nasal drug delivery which requires adhesion to and uptake within the nasal region. Steiner mentions that the microparticles can include a diagnostic imaging agent useful for imaging the nasal tract. However, these microparticles are administered orally or through a needle for intravenous administration (col. 13, lines 14-24 and col. 11, line 65 until col. 12, line 4 and col. 12, lines 20-22), not via inhalation. Imaging the nasal tract is very different from drug delivery through the nasal mucosa. In diagnostic imaging, the imaging agent is administered orally or intravenously and travels through the body emitting signals that are recorded and transformed into a desired "image." Formulations which are suitable for injection are administered in solution, in a volume that suspends the particles so that they are readily distributed at the site of administration. In contrast, in nasal drug delivery the drug is absorbed through the nasal mucosa where it acts locally, and may also be distributed systemically in the body. A formulation suitable for nasal administration cannot be suspended in a quantity of liquid, since this would wash away the particles from the site of deposition. Therefore, Steiner does not disclose or suggest all of the elements of the claimed invention.

Steiner does not disclose drug delivery systems suitable for nasal administration nor suggest a composition of microparticles having an average size between 10 and 20 microns. Steiner does not disclose or suggest modifying the particles for administration in a dry powder form to the nasal mucosa. Thus Steiner does not provide the necessary motivation to one of ordinary skill in the art to modify its particles so that they are suitable for nasal administration. Therefore independent claim 1 and dependent claims 2, 4 and 5 are non-obvious over Steiner.

Claims 7, 9, 11 and 12

Independent claim 7 and its dependent claims define a drug delivery device for nasal administration. Claim 7 specifies that the device contains a device for delivering a measured dose of the drug to the nasal mucosa. Steiner does not disclose or suggest a device for delivering a measured dose of a drug to the nasal mucosa. The only drug delivery devices disclosed by Steiner are ampoules, disposable syringes, and multiple dose vials made of glass or plastic, which are suitable for delivering a drug parenterally (see col. 11, lines 60-63). Steiner notes that drugs may be administered topically in the form of an ointment or cream (see col. 13, lines 1-2) or may be injected subcutaneously, intramuscularly or into the peritoneum using a standard gauge needle (see col. 12, lines 43-52). None of the devices or methods of administration disclosed in Steiner are suitable for delivering a measured dose of the drug to the nasal mucosa, as required by claim 7 and its dependent claims. Further Steiner does not suggest using a device suitable for administering a drug to the nasal mucosa. Therefore, claims 7, 9, 11 and 12 are non-obvious over Steiner.

Claims 14, 15, 17, and 18

Independent claim 14 and its dependent claims define a method for administering a drug to the nasal region of a patient. Claim 14 specifies that the method requires nasally administering a dry powder suitable for nasal administration. Steiner does not disclose or suggest nasally administering a dry powder. Steiner discloses a variety of other methods of administration, such as oral administration (see col. 11, line 66 until col. 12, line 4), topical

administration of an ointment of cream (see col. 12, line 60 until col. 13, line 2), and parenteral administration (see col. 11, lines 61-63). As noted above, the only reference to the nasal tract occurs when Steiner mentions that microparticles can include a diagnostic imaging agent useful for imaging the nasal tract. However, Steiner does not disclose the form in which the microparticles are administered to image the nasal tract. Further, Steiner does not suggest nasal administration of a dry powder. Therefore, claims 14, 15, 17, and 18 are non-obvious over Steiner.

(ii) Rejection of claims 3, 8, 10, 16, 20, and 21 under 35 U.S.C. § 103(a) as being obvious over Steiner, in view of U.S. Patent No. 5,690,954 to Illum ("Illum").

Steiner

Steiner does not disclose antihistamines. Steiner does not disclose drug delivery devices for nasal administration. Steiner does not disclose spray drying. As mentioned above, Steiner does not disclose drug delivery systems suitable for nasal administration. Steiner does not mention nor suggest a composition of microparticles having an average size between 10 and 20 microns. Further, there is no suggestion in Steiner to modify the particles so that they can be administered in a dry powder form and/or to the nasal mucosa.

Illum

Illum describes improving the bioavailability of high molecular weight drugs that are administered to the nasal cavity for systemic delivery (see col. 1, lines 15-18 and col. 4, lines 3-5). Illum addresses the problems of decreased efficiency of nasal drug delivery due to rapid

clearance of nasal sprays and inefficient drug absorption in the nasal cavity by designing a bioadhesive microsphere delivery system that contains absorption enhancers. The bioadhesive microspheres adhere to the nasal mucosa upon contact by forming a gel (col. 3, lines 2-9) and have improved bioavailability due to the presence of absorption enhancers which increase the bioavailability of the drug (col. 4, lines 6-12). Illum discloses materials to increase bioavailability including lysophosphatides, phospholipids, and bile salts. Illum does not disclose or suggest the inclusion of diketopiperazines in the delivery system. Illum discloses microparticles with a size range between 10 and 100 microns (col. 6, lines 13-15). Illum does not suggest the selection of particles having a narrow size range of between 10 and 20 microns.

Steiner and Illum

There is no teaching to combine Steiner and Illum. Illum describes bioadhesive microspheres that form a gel upon contact with nasal mucosa (col. 3, lines 2-9 and col. 6, lines 13-15). Illum lists a number of suitable materials for forming the microspheres. All of the listed materials are polymers, such as starch, gelatin, casein, dextrans, alginate, agarose, albumin, collagen, chitosan, polyvinylacetate, and hyaluronic acid esters (col. 6, lines 15-19). Illum does not disclose a non-polymeric material that does not form a gel when placed on mucosal surfaces, such as a diketopiperazine.

Illum emphasizes the importance of bioadhesive systems. These microparticles allow for an increased period of contact with the mucosal surface in the nasal cavity (see col. 5, lines 19-

23 and col. 8, lines 49-51). Thus, Illum teaches away from using microparticles that do not form gels.

In contrast, Steiner discloses microparticles formed of diketopiperazines and an encapsulated drug. Steiner does not disclose or suggest using gel-forming polymers in its drug delivery system. Therefore there is no suggestion in Steiner or Illum to combine these references; and claims 3, 8, 10, 16, 20, and 21 are non-obvious.

Claims 3, 8, 10, and 16

Claims 3, 8, 10, and 16 are not obvious over Steiner in view of Illum. Neither Steiner nor Illum provides a person of ordinary skill in the art with the motivation to combine these references nor is there any indication of a reasonable likelihood of success. Steiner discloses oral or intravenous delivery of small microparticles having sizes ranging between 0.1 and 10 microns. In contrast, Illum is directed to particles with larger diameters, ranging between 10 and 100 microns, which may be administered to the nasal mucosa for drug delivery. Illum's microparticles are bioadhesive and form gels upon delivery to a mucosal surface (col. 6, lines 15-16). The MPEP explains that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combinations" (MPEP § 2143.01, quoting *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990)). There is no disclosure or suggestion in Steiner to modify its particles so that they are larger (having an average size between 10 and 20 microns), and Illum does not suggest the selection of particles having a narrow size range between 10 and 20 microns. There is no

suggestion in Steiner to modify its particles so that they can be administered in a dry powder form to the nasal mucosa. Furthermore, Illum does not suggest modifying its bioadhesive microparticles to include diketopiperazines and not require the formation of a gel. Thus Steiner and Illum do not provide the necessary motivation to one of ordinary skill in the art to combine these references because neither Steiner nor Illum suggest the desirability of the combination and neither reference provides a reasonable expectation of success. Indeed, Illum teaches away from what Appellants claim by teaching the criticality of a bioadhesive gel to obtain nasal delivery. Thus, one of ordinary skill in the art would not be motivated to combine Steiner with Illum.

Even if one of ordinary skill in the art combined Steiner with Illum, claims 3, 8, 10, and 16 would not be obvious. Illum does not cure the deficiencies of Steiner. First, Illum discloses a broad range of diameters for the particles and does not suggest the selection of particles having a narrow size range of between 10 and 20 microns. Second, Illum discloses that microsphere delivery systems for drug delivery through the nasal mucosa must be both bioadhesive and contain absorption enhancers to increase the bioavailability of the drug to be delivered. In contrast, Appellants have disclosed a different drug delivery system, one which requires the use of diketopiperazines and does not require the formation of a gel. There is no suggestion in Illum to modify the bioadhesive microparticles to include diketopiperazines and not require the formation of a gel. Thus, claims 3, 8, 10, and 16 would not be obvious over Steiner in view of Illum.

Claims 20 and 21

For the reasons discussed above, claims 20 and 21 would not be obvious over Steiner in view of Illum. Further, neither Steiner nor Illum disclose forming the microparticles by spray drying as defined by claims 20 and 21. Illum discloses forming microspheres by emulsion and phase separation methods, followed by chemical crosslinking (see col. 6, lines 22-67). Steiner discloses forming the microparticles via precipitation (see col. 9, line 55 until col. 10, line 9). Therefore the combination of Steiner with Illum would not make claims 20 and 21 obvious.

(9) SUMMARY AND CONCLUSION

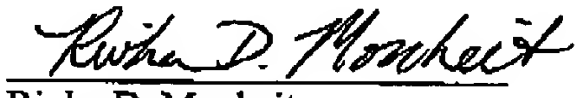
Claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17, and 18 are not obvious over Steiner. Steiner does not disclose or suggest all of the elements of the claimed invention. Steiner does not disclose or suggest drug delivery systems suitable for nasal administration, microparticles having an average size between 10 and 20 microns, or dry powder formulations. The formulations that are disclosed would not be suitable since they must be suspended in an aqueous medium for injection. Thus Steiner does not provide the necessary motivation to one of ordinary skill in the art to modify its particles so that they are suitable for nasal administration. Therefore claims 1, 2, 4, 5, 7, 9, 11, 12, 14, 15, 17, and 18 are not obvious over Steiner.

Claims 3, 8, 10, 16, 20, and 21 are not obvious over Steiner in view of Illum. Neither Steiner nor Illum provides a person of ordinary skill in the art with the motivation to combine these references. There is no disclosure or suggestion in Steiner to modify its particles so that they are larger (having an average size between 10 and 20 microns) or so that they can be

administered in a dry powder form to the nasal mucosa. There is no suggestion in Illum to select particles having a narrow size range between 10 and 20 microns or to modify its bioadhesive microparticles to include diketopiperazines and not require the formation of a gel. Thus Steiner and Illum do not provide the necessary motivation to one of ordinary skill in the art to combine these references. Therefore, claims 3, 8, 10, 16, 20, and 21 are not obvious over Steiner in view of Illum.

For the foregoing reasons, Appellants submit that claims 1-5, 7-12, 14-18, 20 and 21 are patentable.

Respectfully submitted,



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Claims Appendix: Claims On Appeal

1. (previously presented) A composition for the nasal administration of a drug in a dry powder form suitable for administration to the nasal region,

the dry powder form comprising microparticles having an average particle size of between 10 and 20 microns and comprising the drug and diketopiperazines.

2. (original) The composition of claim 1 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

3. (original) The composition of claim 2 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

4. (previously presented) The composition of claim 1 wherein the diketopiperazine is a substitution derivative selected from the group consisting of diketomorpholines, diketooxetanes and diketodioxanes.

5. (previously presented) The composition of claim 1 wherein the diketopiperazine diketopiperazine is formed by cyclodimerization of amino acid ester derivatives.

6. (canceled).

7. (previously presented) A drug delivery device for nasal administration comprising

a drug in a dry powder form in a dosage formulation for administration to the nasal region, and

a device for delivering a measured dose of the drug to the nasal mucosa,

wherein the dry powder form comprises microparticles having an average particle size of between 10 and 20 microns and comprising the drug and diketopiperazines.

8. (original) The device of claim 7 wherein the device is a nasal insufflator.

9. (original) The device of claim 7 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

10. (original) The device of claim 7 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

11. (previously presented) The device of claim 7 wherein the diketopiperazine is a substitution derivative selected from the group consisting of diketomorpholines, diketooxetanes and diketodioxanes.

12. (previously presented) The device of claim 7 wherein the diketopiperazine diketopiperazine is formed by cyclodimerization of amino acid ester derivatives.

13. (canceled).

14. (previously presented) A method of administering a drug to the nasal region of a patient in need thereof, comprising nasally administering a dry powder suitable for nasal administration,

wherein the dry powder form comprises microparticles having an average particle size of between 10 and 20 microns and comprising the drug and diketopiperazines.

15. (original) The method of claim 14 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

16. (original) The method of claim 14 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

17. (previously presented) The method of claim 14 wherein the diketopiperazine is a substitution derivative selected from the group consisting of diketomorpholines, diketooxetanes and diketodioxanes.

18. (previously presented) The method of claim 14 wherein the diketopiperazine diketopiperazine is formed by cyclodimerization of amino acid ester derivatives.

19. (canceled).

20. (previously presented) The composition of claim 1 formed by spray drying.

21. (previously presented) The device of claim 7 wherein the microparticles are formed by spray drying.

Evidence Appendix

No evidence is submitted with the appeal brief.

Related Proceedings Appendix

None

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